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Case Study

Another case of virologically confirmed zoster sine herpete, with electrophysiologic correlation

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A third virologically-confirmed case of thoracic-distribution zoster sine herpete is reported. Electromyography (EMG) of paraspinal muscles demonstrated frequent fibrillation potentials restricted to chronically painful thoracic root segments. Treatment with intravenous acyclovir and oral famciclovir were ineffective. These findings suggest the usefulness of EMG of muscles corresponding to painful dermatomes, combined with virologic studies, to support the diagnosis of zoster sine herpete.

Keywords: zoster sine herpete; EMG; PCR

The detection of varicella zoster virus (VZV) DNA by polymerase chain reaction (PCR) in human cerebrospinal fluid (CSF) and blood mononuclear cells (MNCs), followed by the successful treatment of two subjects with intravenous acyclovir, provided strong support for the nosologic entity of zoster sine herpete (i.e., shingles or zoster without rash) (Gilden *et al*, 1994). We have since identified and treated another patient with virologically proven zoster sine herpete, and for the first time, used electrophysiologic correlation to aid in diagnosis.

The patient was a 75-year-old man who had experienced right-sided, mid-thoracic distribution back pain for 11 years followed by numbness and tingling in both feet for 5–6 years. In May 1992, he had a suprapubic prostatectomy for adenocarcinoma of the prostate. Prostate-specific antigen levels have been normal since then. In March 1994, pin prick, vibratory and light touch sensations were decreased in the feet, and vibratory and cold sensations were decreased at T10–12 on the right, consistent with a ganglioneuropathy. Extensive medical and neurological laboratory testing for evaluation of this ganglioneuropathy did not reveal diabetes, systemic vasculitis, malignancy or nerve root compression.

CSF and blood were processed as described (Yamamoto *et al*, 1991; Mahalingam *et al*, 1995). Oligonucleotide primers (Operon Inc., Alameda, CA) specific for VZV gene 29 were used in PCR amplification with control DNA from uninfected and VZV-infected BSC-1 cells as described (Gilden *et al*, 1992). In March, 1994, PCR did not reveal VZV DNA in his CSF, but in July 1994, PCR revealed VZV DNA in his blood MNCs. The combination of clinical ganglioneuropathy and the presence of VZV DNA in blood led to treatment with famciclovir, 500 mg orally, four times per day for 2 months, unfortunately without relief of pain.

In December 1994, an EMG revealed chronic bilateral mid-thoracic paraspinal denervation with reinnervation at T7-8, manifested by rapid and discrete firing complex polyphasic potentials (up to 22 phases) of markedly increased duration. Flanking T5-6 and T9-10 paraspinal myotomes were normal bilaterally. Superimposed active motor denervation was present in the right T7 myotome only, manifested by frequent (3+) fibrillations and positive sharp waves. Compared to nerve conduction and EMG results in 1989, there had been progression from 'mild to moderate' to 'moderately severe' in the axonal sensory and motor polyneuropathy. In July 1995, a repeat EMG of bilateral T7-8 paraspinal muscles confirmed the December 1994 findings. Among bilateral T5-10 intercostal muscles tested in mid-axillary lines, chronic partial denervation with reinnervation was seen bilaterally at T7-8 as long duration rapid firing polyphasic potentials. Reliable side-to-side comparison of intercostal nerve conductions was precluded by an anterior abdominal surgical scar orientated obliquely across the myotomes of interest.

In March 1995, the CSF was acellular with a normal protein and glucose content. A quantitative enzyme immunoassay for IgG antibody to VZV (Forghani, 1986) was 1.05 in the CSF (normal <1.0); in CSF samples from ten patients with multiple sclerosis, IgG antibody to VZV was <0.5

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in eight subjects, 0.70 in one and 0.86 in one. Over the years, treatment with multiple non-steroidal anti-inflammatory agents, tricyclic antidepressants, a TENS unit, and various narcotics did not relieve his pain. Treatment with oral famciclovir (500 mg four times daily for 2 months), followed by intravenous acyclovir (15 mg per kg three times daily for 14 days), did not relieve pain. He is currently taking oral famciclovir (500 mg four times per day).

We describe a third case of virologically-confirmed zoster sine herpete in a 75-year-old man with a 10-year history of severe thoracic radiculopathy and slowly progressive axonal sensory and motor peripheral neuropathy in the absence of rash. The CSF and an MRI of the thoracic spine were normal. VZV DNA was found in his blood MNCs, and he was treated with oral and intravenous acyclovir. Despite treatment, antibody to VZV was found in his CSF 9 months later.

Other pertinent clinical features included a past history of adenocarcinoma of the prostate, a peripheral neuropathy, and a lack of response to antiviral therapy. Because this is only the third case of virologically confirmed zoster sine herpete, the significance, if any, of prostate cancer in this patient and in one of the two subjects previously reported (Gilden *et al*, 1994) remains unclear. The ganglioneuropathy in both of the original two subjects with zoster sine herpete was restricted to the thoracic region, but our patient had both a thoracic radiculopathy and a peripheral neuropathy. While the VZV etiology of our patient's peripheral neuropathy cannot be confirmed antemortem, the combined radiculopathy and neuropathy is reminiscent of the more severe fatal VZV meningoradiculitis without skin lesions reported by Dueland *et al* (1991), as well as the VZV meningoradiculoneuritis described by Snoeck *et al* (1994) in which progression of the neuropathy was not associated with skin lesions.

Because thoracic muscles are not readily testable during neurologic examination, the incidence of motor denervation after thoracic-distribution zoster is unknown. However, thoracic muscles were previously studied by EMG in two cases and revealed chronic denervation in myotomes corresponding to thoracic-distribution zoster (Gardner-Thorpe *et al*, 1976). Our subject reported herein extends the range of EMG abnormalities to include frequent fibrillations and positive sharp waves, indicative of acute or persistent denervation, including the first EMG documentation of active motor denervation in virologically confirmed zoster sine herpete. Thus, EMG of muscles corresponding to painful dermatones may be useful to support the diagnosis and treatment of zoster sine herpete.

Finally, unlike the gratifying response to intravenous acyclovir in the first two zoster sine herpete patients (Gilden *et al*, 1994), our patient did not respond to aggressive antiviral treatment with oral famciclovir followed by 14 days of intravenous acyclovir. While the lack of response to acyclovir might be interpreted as atypical, too few cases of zoster sine herpete have been studied to allow statistical analysis of treatment. The first two virologically confirmed cases of zoster sine herpete had experienced pain for 6–8 months before successful treatment, while our patient had pain for 11 years. If zoster-associated pain is related to the presence of a greater virus burden in ganglia of patients compared to the low levels present during latency (Mahalingam *et al*, 1993), it is possible, if not likely, that virus-induced neuronal damage would be far greater after 11 years than after 6–8 months. Thus, the chances of success after short-term treatment with anti-herpesvirus drugs would be reduced. Nevertheless, because his blood MNCs contained VZV DNA and his CSF contained antibody to VZV, indicative of continued productive virus infection in the nervous system, our patient is currently being maintained on oral famciclovir. A rationale for continued therapy is further supported by the detection of VZV DNA in blood MNCs from 11 of 15 elderly patients with postherpetic neuralgia (pain which persists months to years after the disappearance of zoster rash), but not in any of the 19 zoster patients without postherpetic neuralgia, nor in any of 11 elderly individuals without a history of zoster (Mahalingam *et al*, 1995). The hypothetical presence of a greater virus burden in ganglia of patients with either postherpetic neuralgia or zoster sine herpete compared to the low levels present during latency (Mahalingam *et al*, 1993), raises the possibility that MNCs trafficking through these productively-infected ganglia, encounter and engulf virus whose DNA can be amplified by PCR.

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